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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 05/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/932,451	OZAWA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,12,15,24,26-29,35,41 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,12,15,24,26-29,35,41,42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on ____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Final Rejection

Claims 1, 7, 12, 15, 24, 26-29, 35 and 41-42 are pending.

Applicant's traversal, the amendment to claims 15 and 35, the cancellation of claim 23, and the addition of claims 41 and 42 filed on 2/22/05 is acknowledged and considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7, 12, 24, 26, 29, and 35 remain and claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., (US 2003/0148968) taken with Gao et al. (WO 02/02148) in further view of Colosi (US Patent 6,004,797).

Hammond teaches a method of treating a patient with a peripheral vascular disease (e.g., ischemic skeletal muscle) comprising a vector construct containing a gene encoding an angiogenic protein (pages 1, 4, 5, 8, 9, 11, 12, and 19). The vector used in the invention can be a viral vector for example an adeno-associated virus (AAV) (page 8). Hammond teaches that the viral vector stock will contain few if no wild type virus (page 8). The vector comprising a transgene coding for angiogenic protein or peptide, such as, FGF-2, FGF-5, FGF-4, aFGF, and/or a VEGF including VEGF-165 (pages 8 and 9). Hammond teaches that other angiogenic proteins can be used in the method, such as angiopoietins (page 9). Hammond teaches increasing the blood flow to the affected (e.g., ischemic) region of the tissue and/or muscle (page 8). Hammond teaches that angiogenic proteins produce blood vessels (page 6). Hammond teaches using a catheter into a blood vessel that supplies blood to the muscle in the leg (page 16). However, Hammond does not specifically teach using rAAV virions, which are free of wild-type AAV virions and helper virus. In addition, Hammond does not specifically teach using about

10^{10} to about 10^{15} of rAAV virions in the method to express the angiogenic factor(s) at a therapeutic level.

However, at the time the invention was made, Gao teaches a method of promoting angiogenesis in a patient delivering to a region of tissue, such as ischemic tissue by intramuscular injection a recombinant vector comprising at least two transgenes encoding angiogenic proteins (pages 4-5 and 69). Gao recites a list of various angiogenic proteins including VEGF (e.g., VEGF-165, FGF (e.g., FGF-2) and Angs (Ang-1) that could be used in the method (pages 5-7, 21-22, and 24). Gao teaches that FGFs and Angs are known to stimulate VEGF (pages 21). Gao teaches using AAV vectors in the methods (pages 34-36, 40-41, 51 66, and 70). Gao teaches that an effective dose of the viral vectors will typically be in the range from 10^5 and 10^{13} viral particles, more particularly 10^7-10^{10} viral particles (page 48). However, Gao does not specifically teach does not specifically teach using rAAV virions, which are free of wild-type AAV virions and helper virus.

In addition, at the time the invention was made, Colosi teaches adenovirus helper-free recombinant AAV virion production was routine to one of ordinary skill in the art (column 5, lines 1-3, column 40, claim 10). Colosi teaches that infectious AAV and helper virus are undesirable for several reasons, safety and health concerns and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields (column 3, lines 7-18). Colosi teaches that AAV has a wide host range (column 1, lines 45-46).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond taken with Gao in further view of

Colosi to use the rAAV virions taught by Colosi to treat an ischemic condition in the mammal, wherein the rAAV virions comprises a nucleotide sequence encoding angiogenic factor(s). One of ordinary skill in the art would have been motivated to use the rAAV virions taught by Colosi because rAAV virions are well known in the art for use in therapeutic methods. In addition, one ordinary skill in the would have been motivated to use the rAAV virions taught by Colosi to avoid safety and health concerns when delivering rAAV virions to an animal and concomitant production of helper virus particles in rAAV virion producing cells diverts large amounts of cellular resources away from rAAV virion production, resulting in lower rAAV virion yields.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond taken with Gao in further view of Colosi to use the rAAV virions at about 10^5 to about 10^{13} in the method. One of ordinary skill in the art would have been motivated to use the rAAV virions at about 10^5 to about 10^{13} in the method because Gao teaches using an effective dose of the viral vectors will be in this range. In addition, a *prima facie* case of obviousness exist because the titer of viral particles taught by Gao overlaps with the amount of virions used in the claimed method and the applicants do not teach that the amount of virions used in the claimed method is a critical part of their invention. See MPEP 2144.05.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond taken with Gao in further view of Colosi to use the rAAV virions comprising at least two angiogenic factors in the method. One of ordinary skill in the art would have been motivated to use at least two

angiogenic factors in the method to improve the method and because Gao and Hammond teach using at least two angiogenic factors in the method.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/22/05 have been fully considered but they are not persuasive.

Applicants argue that because provisional application 60,226,056 included data obtained 10-weeks after injection (pages 2, 9, 10 and 12), injection must necessarily have taken place before 6/8/00 which is before Gao's earliest priority date of June 30, 2000.

Applicant's argument is not found persuasive because an affidavits or declarations under 37 CFR 1.131 is required to overcome a prior art rejection and applicants have not provide an affidavit or declaration under 37 CFR 1.131. See MPEP 715, III. The WO02/02148 document is considered prior art under 102(e) and has priority to U.S. application 09/607,766, which provides support for the subject matter used in the prior art rejection over the instant claims. See entire specification of '766.

Claims 7 and 15 remain and claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., (US 2003/0148968) taken with Gao et al. (WO 02/02148) in further view of Colosi (US Patent 6,004,797) as applied to claims 1, 12, 23, 24, 26, 29, and 35 above, and further in view of Takeshita et al., (Biochemical and Biophysical Research Communications 227:628-635, 1996).

However, Hammond, Gao and Colosi do not specifically teach using a gene encoding VEGF-165 in the method of treating an ischemic condition in the skeletal muscle.

However, at the time the invention was made, Takeshita teaches that in vivo gene transfer of VEGF-165 achieves therapeutic angiogenesis (page 628).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond, Gao, and Colosi in further view of Takeshita to use a gene encoding VEGF-165 in the method. One of ordinary skill in the art would have been motivated to use a gene encoding VEGF-165 in the method because a gene encoding VEGF-165 is known to achieve therapeutic angiogenesis in a subject having an ischemic limb.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/22/05 have been fully considered but they are not persuasive for the reasons set forth under the prior response to applicant's argument.

Claim 27 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., (US 2003/0148968) taken with Gao et al. (WO 02/02148) in further view of Colosi (US Patent 6,004,797) as applied to claims 1, 12, 23, 24, 26, 29, and 35 above, and further in view of Vuorela et al., (Molecular Human Reproduction, 6:276-282, March 2000) and Levine et al., (US 2002/0019350).

Gao teaches that Angs are known to stimulate VEGF (pages 21). However, Hammond, Gao and Colosi do not specifically teach using a gene encoding VEGF and a gene encoding Ang-1 in the method of treating an ischemic condition in the skeletal muscle.

However, at the time the invention was made, Ang-1 was known to one of ordinary skill in the art to stimulate Tie-2 receptor (Vuorela, supra) and Tie-2 receptor is a receptor for VEGF (Levine, page 3).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond, Gao, and Colosi in further view of Vuorela and Levine to use a gene encoding VEGF and a gene encoding Ang-1 in the method. One of ordinary skill in the art would have been motivated to use a gene encoding VEGF and a gene encoding Ang-1 in the method because the expression of Ang-1 would stimulate the expression of VEGF in the ischemic tissue an increase the therapeutic effect of VEGF in the tissue.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/22/05 have been fully considered but they are not persuasive for the reasons set forth under the prior response to applicant's argument.

Claim 28 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Hammond et al., (US 2003/0148968) taken with Gao et al. (WO 02/02148) in further view of Colosi (US

Patent 6,004,797) as applied to claims 1, 12, 23, 24, 26, 29, and 35 above, and further in view of Asahara et al., (Circulation. 1995; 92(9 Suppl):II365-71).

Gao teaches that FGFs are known to stimulate VEGF (pages 21). However, Hammond, Gao and Colosi do not specifically teach using a gene encoding VEGF and a gene encoding FGF-2 in the method of treating an ischemic condition in the skeletal muscle.

However, at the time the invention was made, vascular endothelial growth factor and basic fibroblast growth factor (bFGF or FGF-2) were to one of ordinary skill in the art to have a synergistic effect on angiogenesis in vivo (Asahara, page 365).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Hammond, Gao, and Colosi in further view of Asahara to use a gene encoding VEGF and a gene encoding FGF-2 in the method. One of ordinary skill in the art would have been motivated to use a gene encoding VEGF and a gene encoding FGF-2 in the method because both factors were known to have a synergistic effect on angiogenesis in vivo (page 365).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 2/22/05 have been fully considered but they are not persuasive for the reasons set forth under the prior response to applicant's argument.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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AU1632